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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAPUST, RACHEL B	

ART UNIT	PAPER NUMBER
1647	21

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/577,084	OZAWA ET AL.	
	Examiner	Art Unit	
	Rachel B. Kapust	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *9 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 10-18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I with traverse in paper no. 18 and election of c-mpl, without traverse, is acknowledged. Applicant's argument that Groups I, III, V, and VI should properly be grouped together is found to be persuasive. Thus claims 1-8, 10-18, and 20, formerly Groups I, III, V, and VI, are rejoined and examined in light of Applicant's election of c-mpl as a species.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Specification

The disclosure is objected to because of the following informalities:

The character spacing of the first full paragraph on page 4 is incorrect. For example, the word "receptor" ends on the third line as "recepto" and the "r" follows on the next line. A substitute paragraph is required to correct the character spacing.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10-18, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is drawn to a "domain that *associates* when a ligand binds to the domain" (emphasis added). It is not clear whether "associates" means the ligand binding to the ligand-binding domain or whether "associates" is meant to be the dimerization of a ligand-binding domain. If Applicants mean the latter, amending the claim to read "a domain that dimerizes" could obviate the rejection so long as there is written support in the specification. Claims 2-8, 10-18, and 20 are rejected as being dependent on claim 1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 10-18, and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for chimeric proteins comprising an estrogen receptor domain and c-mpl domain, does not reasonably provide enablement for chimeric proteins comprising any ligand-binding domain or any cytokine receptor or any part of a cytokine receptor that imparts proliferation activity to a cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention; 2) state of the prior art; 3) relative skill of those in the art; 4) level of predictability in the art; 5) existence of working examples; 6) breadth of claims; 7) amount of direction or guidance by the inventor; and 8) quantity of experimentation needed to make and/or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Applicants state "any ligand can be used in the present invention as long as it acts on a specific protein to cause association of the protein (p. 6). Applicants further state "any cytokine receptor can also be used...as long as it imparts proliferation activity to a cell" (p. 7). Examples of cytokine receptors listed were G-CSF receptors, c-mpl, and members of the tyrosine kinase receptor family. Moreover, it is possible to use only a domain of the cytokine receptor that imparts proliferating activity to a cell (p. 7).

Of the domains used in the working examples, Applicants only give an example of a portion of the G-CSF receptor that imparts a proliferating activity to a cell. Applicants have not provided any examples of other portions of cytokine receptors that impart a proliferating activity to a cell. The amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be deleted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Certain positions in the sequence are critical to

the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites.

As previously mentioned, the claims encompass any cytokine receptor that imparts a proliferation activity to a cell. Although many cytokine receptors induce cell proliferation, it is not a universal function of all cytokine receptors. For instance, transforming growth factor β (TGFβ) receptors, when activated, can lead to growth inhibition (see Wimmel *et al.* (2003) *Gut* 52: 1308-1316 and Chui *et al.* (2003) *J. Hepatology* 39: 731-737). Interferon-γ (IFN-γ) receptors, when activated, inhibit cell proliferation and can actually induce apoptosis (see Kakuta *et al.* (2002) *Immunology* 105: 92-100). IL-10 is able to inhibit macrophage proliferation (O'Farrell *et al.* (1998) *EMBO* 17(4): 1006-1018). Similarly, not all ligand-binding domains dimerize when bound to an appropriate ligand. Some form heterodimers while others do not dimerize at all (see Marcinkowska *et al.* (2002) *Acta Biochimica Polonica* 49(3): 735-745). Because of the varied functions of cytokine receptors, one of skill in the art would not know whether a cytokine receptor will induce cell proliferation until the gene is cloned and expressed. In addition, because not all ligand-binding domains dimerize, one of skill in the art would not know whether a ligand will induce dimerization of the domain until the chimeric gene is cloned and expressed.

Since detailed information regarding the structural and functional requirements of the portions of cytokine receptors is lacking, the state of the prior art, the unpredictability of the art, the lack of working examples, the breadth of the claims, and the lack of direction provided by the Applicants, it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification.

Claims 1-8, 10-18, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant disclosure of a few ligand-binding domains and a few cytokine receptors does not adequately describe the scope of the claimed genus, which encompasses hundreds of different fusion proteins with varying structures and functions. The fusion protein claims comprises a ligand-binding domain, a domain that associates when a ligand binds to the ligand-binding domain, and a domain comprising a cytokine receptor or a part thereof that imparts proliferation activity to a cell. The specification defines the DNA sequences and the fusion proteins to which its claims are directed exclusively in terms of the function of the separate domains of the fusion protein. The specification at best enables and invites persons skilled in the art to identify those fusion proteins which function in the manner desired.

While Applicants teach the manner and means by which the fusion proteins may be constructed (see p. 12-13), a person of ordinary skill in the art would not be able to visualize or recognize the identity of the full scope of fusion protein sequences claimed. Neither the functional characteristics of the fusion proteins encoded by the claimed DNA nor prior art knowledge of the structure of the amino acid sequences of many of the protein domains forming the fusion proteins or nucleotide sequences which encode the proteins, allow persons of ordinary skill in the art to visualize or recognize the full scope of the biological materials claimed.

In order to visualize or recognize the full scope of the biological materials claimed, a person having ordinary skill in the art is required to perform one or more tasks, utilize one or more skills, to determine the complete identity of those biological materials reasonably expected to perform the functions the claims require, obtain those materials, and confirm their expectations for those materials. Only after persons skilled in the art prepare new DNA and test that DNA for fusion protein functionality will they know whether Applicants would have the right to exclude them from making and using the new DNA constructs that they prepared. Therefore, the specification does not provide an adequate written description of the subject matter claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 6-8, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Gurney *et al.* (1995, *Proc. Natl. Acad. Sci. USA* 92: 5292-5296, submitted by Applicants in June 20, 2003 IDS). Gurney *et al.* teach a chimeric receptor, the growth hormone receptor (GHR) fused to c-Mpl (p. 5292, column 2). Gurney *et al.* further teach that the chimeric receptor induced cell proliferation in response to growth hormone (p. 5293, column 2). Moreover, Gurney *et al.* teach that growth hormone induces homodimerization of the GHR, and homodimerization of c-Mpl is sufficient for receptor activation (p. 5296, column 1). Thus, claims 1-3, 6-8, and 20 are anticipated by Gurney *et al.*

Claims 1, 6-8, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Maruyama *et al.* (1994, *J. Biol. Chem.* 269(8): 5976-5980).

Maruyama *et al.* teach chimeric receptors carrying the extracellular domain and the transmembrane domain of the epidermal growth factor receptor (EGFR) linked to either the full-length or membrane proximal half of the cytoplasmic domain of the erythropoietin receptor (EPOR) (p. 5977). The EPOR belongs to the cytokine receptor superfamily, and it is activated by dimerization or oligomerization. The EPOR is also known to transmit ligand-dependent proliferation signals (p. 5978, column 2). Maruyama *et al.* teach EGF induced cell proliferation in cells containing the chimeric receptors (p. 5978), column 2). EGF induced dimerization of the EGFR, which resulted in activation and dimerization of the EPOR (p. 5979, column 1). Thus, claims 1, 6-8, and 20 are anticipated by Maruyama *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gurney *et al.* as applied to claims 1-3, 6-8, and 20 above, and further in view of Wang *et al.* (1995, *J. Biol. Chem.* 270(40): 23322-23329). As discussed above, Gurney *et al.* teach a chimeric receptor comprising GHR fused to c-Mpl. Gurney *et al.* also teach that growth hormone induces homodimerization of the GHR, and homodimerization of c-Mpl is sufficient for receptor activation (p. 5296, column 1). However, Gurney *et al.* do not the use of an estrogen receptor instead of GHR.

Wang *et al.* teach that the estrogen induces homodimerization of estrogen receptors (p. 23323, column 1). Considering that estrogen receptors are able to form homodimers after binding to estrogen, a person of ordinary skill in the art would have expected that estrogen receptors would be a useful substitution for the GHR as taught by Gurney *et al.* Because estrogen receptors form homodimers after binding to estrogen, a person of ordinary skill in the art would have been motivated to combine the teachings of Gurney *et al.* and Wang *et al.* Accordingly, the invention taken as a whole is *prima facie* obvious over the prior art.

NO CLAIMS ARE ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel B. Kapust whose telephone number is (703) 305-0634. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RBK